UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/023,441	12/18/2001	Martin J. Jacobs	CP216	2296

7590 05/06/2003

Robert T. Hrubiec
Cephalon, Inc.
145 Brandywine Parkway
West Chester, PA 19380

EXAMINER
MAIER, LEIGH C

ART UNIT	PAPER NUMBER
1623	8

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/023,441	Applicant(s) Jacobs
	Examiner Leigh Maier	Art Unit 1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-48* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Apr 15, 2002* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5, 7*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Claims

Claims 1-48 are pending..

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5, 10-13, 15-20, 24, 29-31, 35, 36, 38, 39, 41, 42, 46, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by NGUYEN et al (US 5,843,347) with HEDGES (Chem. Rev., 1998) to support inherency.

NGUYEN discloses the preparation of a complex of modafinil and HP–β–cyclodextrin comprising contacting the modafinil with the HP–β–cyclodextrin (50% by weight relative to the water) and other pharmaceutically acceptable excipients in an aqueous medium. See example 16 with more detailed description of the process in example 1. The composition is lyophilized to obtain a solid product. The intent in preparing the exemplified products is to improve the

bioavailability of the active ingredients. See col 3, lines 30-34 and col 9, beginning line 50 and continuing through col 10, line 3.

Regarding the formation of an inclusion product, HEDGES teaches that one method for the preparation of CD inclusion complexes is the slurry method in which the CD is suspended in water and combined with the desired guest compound. See section bridging pages 2035 and 2036. During the mixing, some CD goes into solution and forms a complex. Therefore, a compound amenable to inclusion formation mixed with a CD in the method disclosed by NGUYEN would produce an inclusion complex, with at least some of the complex in solution (claims 10 and 19).

Regarding the complex being taste-masked, HEDGES teaches that one benefit of preparing CD complexes is that an off-taste of a guest molecule can be reduced or eliminated. See section D, page 2041. An inclusion complex produced by the method of NGUYEN would be taste-masked.

Regarding the blood serum profile, claims 35, 36, 38, 39, and 48 are written broadly with no requirement regarding the amount of composition to be adminstered in order to produce recited blood serum increase/profile. Nor do the claims require any amount of modafinil to which the composition would be compared. For example, a dose of the NGUYEN composition comprising 200 mg of modafinil would provide the recited blood serum level increases over a dose of 100 mg of solid modafinil. The administration of some amount of the NGUYEN composition would produce the blood serum profile of Fig. 1.

Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claims 1-5, 9, 10, 12-19, 21, 24, 25, 28, 35-43, 46, and 48 are rejected under 35 U.S.C. 102(b) as being anticipated by RAMBERT et al (Neuropharmacology, 1994) with HEDGES (Chem. Rev., 1998) to support inherency.

RAMBERT discloses administration of an aqueous solution of modafinil to mice. The modafinil is solubilized using HP–β–cyclodextrin. The reference exemplifies dosages of 100 μg and 200 μg of modafinil in 10 μl of the injection solution. This corresponds to 10 mg/ml and 20 mg/ml, respectively.

Regarding the formation of an inclusion product, HEDGES teaches that one method for the preparation of CD inclusion complexes is the coprecipitation method in which the CD and the desired guest compound are added to solution. See section A, page 2035. Therefore, in the course of solubilizing the modafinil with HP–β–cyclodextrin, an inclusion complex would be formed. This complex would also be taste masked as discussed above.

Regarding the blood serum profile, claims 35-39, and 48 are written broadly with no requirement regarding the amount of composition to be adminstered in order to produce recited

profile. A dose of the RAMBERT composition comprising 200 μg of modafinil would provide the recited blood serum level increases over a dose of 100 μg of solid modafinil. The administration of some amount of the RAMBERT composition would produce the blood serum profile of Fig. 1.

Since the Office does not have the facilities for preparing the claimed materials and comparing them with prior art inventions, the burden is on Applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 9-21, 24, 29-31, 35, 36, 38, 39, 41, 42, 46, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over NGUYEN et al (US 5,843,347).

The invention is drawn to a complex of a modafinil compound and a cyclodextrin. Claim 5 recites a variety of cyclodextrin species.

NGUYEN teaches as set forth above.

The reference does not specifically exemplify the full range of cyclodextrins. However, the reference expressly suggests the use of a wide variety of known cyclodextrins in the products and clearly contemplates the use of any known cyclodextrin. See col 6, lines 50-64.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the exemplified modafinil complex with any of the cyclodextrins suggested by the reference for the art-disclosed utility. One of ordinary skill would expect success in making this modification.

Claims 25-27, 32-34, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over NGUYEN et al (US 5,843,347) as applied to claims 1-5, 9-21, 24, 29-31, 35, 36, 38, 39, 41, 42, 44, 46, and 48 above, and further in view of GREBOW et al (US 5,618,845).

The invention is as set forth above. Dependents recite specific unit doses; the composition in the form of a tablet, capsule, syrup, or elixir; and therapeutic methods.

NGUYEN teaches as set forth above. The reference teaches the preparation of microbeads comprising modafinil having particle size of 2-5 μm. The reference teaches that the product is NGUYEN does not teach specific unit doses; the composition in the form of a tablet, capsule, syrup, or elixir; or therapeutic methods.

GREBOW teaches that modafinil has utility for the treatment of a variety of disorders such as hypersomnia, narcolepsy, sleep apnea, general sleep disorders, Parkinson's disease, and ischemia. See col 1. The reference further teaches the use of unit dosages of 100 mg and 200 mg for humans with a prefered particle size of 2-17 μm. See col 4, lines 11-15 and col 2, lines 50-55. The reference further teaches the administration of the pharmaceutical composition in a variety of forms, such as tablet, capsule, liquid/suspension or emulsion. Liquid/suspensions or emulsions would be recognized by the artisan to be essentially the same as syrups and elixirs.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use the NGUYEN composition for the preparation of tablets, capsules, syrups or elixirs for the administration to patients treatment of the disorders taught by GREBOW. One of ordinary skill would reasonably expect success in using NGUYEN composition for such treatment. It would be further obvious to prepare the composition in unit dosages of 100 mg or 200 mg, as these dosages were taught by GREBOW. It would be further obvious to use this composition to treat any any mammal, such as humans or rats.

Claims 32-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over NGUYEN et al (US 5,843,347) as applied to claims 1-5, 9-21, 24, 28-31, 35, 36, 38, 39, 41, 42, 44, 46, and 48 above, and further in view of (1) LAFON (US 5,391,576); (2) SCAMMELL et al (US 6,455,588); OR (3) MILLER et al (US 6,346,548).

The invention is as set forth above.

NGUYEN teaches as set forth above. The reference does not teach the treatment of the disorders recited in the claims.

LAFON teaches the use of modafinil to treat cerebral ischemia and cerebral infarction (stroke). See abstract.

SCAMMELL teaches the use of modafinil to treat eating disorders and to stimulate appetite. See abstract and col 3, lines 8-16.

MILLER teaches the use of modafinil to treat ADHD. See abstract.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to use an effective amount of modafinil in the form of the NGUYEN composition in order to treat the recited disorders because the art of record, set forth above, taught that this compound has utility for the treatment of these disorders. One of ordinary skill would reasonably expect success in using the NGUYEN composition for this purpose.

Claims 6-8, 22, 23, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over RAMBERT et al (Neuropharmacology, 1994) as applied to claims 1-5, 9, 10, 12-19, 21, 24, 28, 35-43, 46, and 48 above, and further in view of PITHA et al (Int. J. Pharm., 1986).

The invention is as set forth above. Dependents recite CD/modafinil molar ratios; the use of 2–HP–β–cyclodextrin; and a composition comprising modafinil in an aqueous 50% HP–β–cyclodextrin.

RAMBERT teaches as set forth above. The reference is silent regarding the use of *2*–HP–β–cyclodextrin; the molar ratio in the compositions; and the percentage of the HP–β–cyclodextrin.

PITHA teaches that 2–HP–β–cyclodextrin is highly soluble in water and is useful for solubilizing drugs with limited water solubility. See abstract; Fig. 1; and Table 1. The reference teaches that aqueous solutions comprising up to about 75% (w/w) of 2–HP–β–cyclodextrin can be prepared and that solubilites of some compounds in aqueous 2–HP–β–cyclodextrin (40-50% - w/w) were up to three orders of magnitude higher than those in water. See page 79, right column.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the RAMBERT composition using 2–HP–β–cyclodextrin because PITHA had taught that this CD has very high water solubility and has very good solubilizing power for compounds, such as modafinil, with limited water solubility. It would be further obvious to prepare the composition using a 50% solution of 2–HP–β–cyclodextrin as

taught by PITHA. One of ordinary skill would have been motivated to prepare a concentrated solution in order to minimize the volume of the solution to be administered to a patient. It would be within the scope of the artisan to optimize the molar ratio of the components through routine experimentation.

Examiner's hours, phone & fax numbers

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh Maier whose telephone number is (703) 308-4525. The examiner can normally be reached on Monday-Friday 7:00 to 3:30 (ET).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson (703) 308-4624, may be contacted. The fax phone number for Group 1600, Art Unit 1623 is (703) 308-4556 or 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-1235.

Visit the U.S. PTO's site on the World Wide Web at http://**www.uspto.gov**. This site contains lots of valuable information including the latest PTO fees, downloadable forms, basic search capabilities and much more.

Leigh C. Maier
Patent Examiner
May 1, 2003